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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,338	10/31/2003	Birgit Schested Hansen	6443.500-US	2536
23650	7590	07/31/2007		
NOVO NORDISK, INC. PATENT DEPARTMENT 100 COLLEGE ROAD WEST PRINCETON, NJ 08540			EXAMINER KWON, BRIAN YONG S	
			ART UNIT 1614	PAPER NUMBER
			NOTIFICATION DATE 07/31/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com

Office Action Summary	Application No. 10/699,338	Applicant(s) HANSEN ET AL.	
	Examiner Brian S. Kwon	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 May 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5-9, 11, 14-15, 17, 20 and 44-49 is/are pending in the application.
- 4a) Of the above claim(s) 8, 9, 11, 20 and 44-49 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2, 5-7, 14-15 and 17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's filing of an amendment/remarks on 05/14/2007.
2. By the amendment, claims 2, 5-6, 11, 14-15, 17 and 20 have been amended; claims 1, 3-4, 10, 12-13, 16, 18-19 and 21-43 have been cancelled; and claims 44-49 have been newly added.
3. Claims 2, 5-9, 11, 14-15, 17, 20 and 44-49 are currently pending in the application. However, claims 8-9, 11, 20 and 44-49 have been withdrawn from further consideration by examiner as being drawn to a non-elected invention.
4. Claims 2, 5-7, 14-15 and 17 are currently pending for prosecution on the merits of the case.
5. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2, 5-7 and 14-15 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

Art Unit: 1614

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses compounds represented by the formula I having a slope calculated from using measurements from Assay (I) as a suitable example of bioactive agent, which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, the instant claims are directed to encompass “prodrugs” which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these meet the written description provision of 35 USC 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompasses a myriad of possibilities. To the extent that no structure function data is disclosed in connection with theses functionally described compounds to correlate, or there is not disclosed correlation established between these functional drugs and the contemplated desired therapeutic effect to be achieved in practicing the instant invention, the specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116).

With the exception of the compound of the formula I, the skilled artisan cannot envision the detailed chemical structure of the encompassed prodrugs, derivatives, analogs, etc.,

Art Unit: 1614

regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

6. Claims 2, 5-7, 14-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of increasing glucose utilization with a specific compound of the formula I, does not reasonably provide enablement for treating the

Art Unit: 1614

disease conditions with compounds or prodrugs encompassed by the instant invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant invention relates to a method of treating a disease condition benefiting from an enhancement of mitochondrial respiration, namely obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis and cancer, by the administration of the claimed compound(s) represented by the formula I having a slope calculated from an equation or a pharmaceutically acceptable salt, solvate or prodrug thereof.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological Compounds often react unpredictably under different circumstances. *Nationwide Chem. Corp. v. Wright*, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); *Affd* 584

Art Unit: 1614

F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a biological compound is considered to be an unpredictable art and the physiological or pharmaceutical activity of treating "a disease condition benefiting from an enhancement of mitochondrial respiration..." is an unpredictable art.

The claims are very broad due to the vast number of possible diseases conditions that are described as being "a disease condition benefiting from an enhancement of mitochondrial respiration" including "obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis, cancer, endometrial cancer, breast cancer, prostate cancer, colon cancer and the maintenance of a weight loss". Furthermore, the claims are further complicated by plethora of compounds having characteristic of "a slope value calculated from the equation", particularly compounds of the formula (I) or prodrug thereof.

For instance, in cancer therapy art, it is generally recognized that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see Cecil Textbook of Medicine, page 1004). Different types of cancers affect different organs and have different method of growth and harm the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers.

Art Unit: 1614

Furthermore, at the time of the invention was made, it was generally recognized in diabetes therapy art that the intensive blood-glucose control with anti-diabetic substantially decrease the risk of microvasuclar complications, such as retinopathy, neuropathy and nephropathy, but not macrovascular disease such as hypertension, atherosclerosis and cardiovascular outcomes (see Lancet, Vol. 352, Sept. 12, 1998). Thus, it is beyond the skill of pharmacologist today to get an agent to be effective against obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, dyslipidemia, coronary heart disease.

Although some known chemical uncouplers that have activities in increasing the metabolic rate may be useful in treating obesity, it is not known yet that a single underlying mechanism ties together all of the seemingly unrelated manifestation of the disease conditions encompassed (for example, obesity, gallbladder disease and breast cancer). There is no demonstrated correlation or sufficient evidence in the specification or incorporated by reference that increased glucose utilization would be able to treat all the diseases encompassed by the instant claims. Therefore, the skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of sad compounds.

The specification discloses the effects of increased glucose utilization (Figures 1- 3) using the compounds that have a slope value calculated from an equation. However, the specification fails to provide how to make/use the invention commensurate in scope with these claims without undue amount of experimentation. As discussed in preceding comments, in the instant case, only a limited number of "a compound capable of increase glucose Utilization" in

Art Unit: 1614

vitro study is disclosed in the specification, thereby the specification fails to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The instant claims read on any compounds of formula I having "a slope value calculated from the equation" or "prodrugs" thereof, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

As discussed in preceding comments, to practice the instant invention to the claimed scope, applicant would have to (i) make or screen numerous potentially suitable compounds of the formula I characterized as "having a slope value calculated from the equation" or "prodrug" thereof, (ii) undergo assays to find out which compounds are able to exert the desired pharmacological activity, and then (iii) extrapolate the test and result to the claimed therapeutic utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, the limited number of working examples and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would have to undergo an undue amount of experimentation to practice the claimed invention.

Art Unit: 1614

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

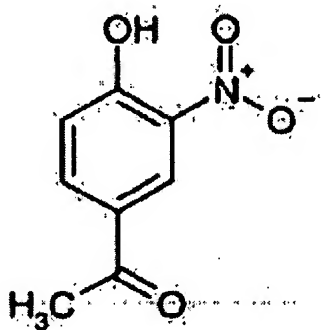
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

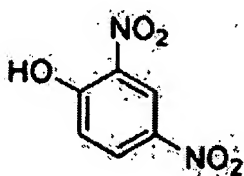
7. Claims 2, 5-7 and 14-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachynsky (US Patent 4,673,691, issue date: Jun. 16, 1987) in view of Batt et al. (US Patent 5,593,994, issue date: Jan. 14, 1997) and Rink et al. (US Patent 5,739,106, issue date: Apr. 14, 1998) as applied to claims 4-7.

Art Unit: 1614

The instant claims are directed to a method comprising the administration of a compound having a slope calculated from an equation as defined in the claim. Further limitation include that the method is for treating a disorders, such as Type II diabetes, obesity, atherosclerosis, hypertension, impaired glucose tolerance, dyslipidemia, coronary heart disease, gall bladder disease, osteoarthritis and cancer, in a patient. A compound for the treatment is the elected species of 4-hydroxy-3-nitroacetophenone having the following structure:



Bachynsky teaches a method of inducing weight loss in a patient comprising administering 2,4-dinitrophenol (DNP) (column 6, lines 20-22) having the following structure:



The prior art teaching differs from the instant invention in that (i) the prior art compound has a nitro group at position 4 whereas the compound of the instant invention has an aceto group at position 4 and (ii) the prior art does not disclose that the obese patient has type II diabetes. However, the base structure of the prior art compound 2,4-dinitrophenol is the same as the base structure of 4-hydroxy-3-nitroacetophenone of the instant invention and the physiological

Art Unit: 1614

activities are analogous. In addition, Batt et al. disclose compounds for treatment where the substitute groups on the benzene ring can be nitro or aceto (column 49, line 39). Therefore, the substitution of a nitro group with an aceto group on the benzene ring is obvious. One having ordinary skill in the art would have been motivated to substitute a nitro group of the prior art compound with an aceto group with the expectation that the substitution would not significantly alter the analogous properties of the compound due to close structural similarity of the compounds. See *In re Grunwell*, 203 USPQ 1055. With respect to the patient population for treatment in claims 4-7 where the patient who is obese is suffering from type II diabetes, Rink et al. disclose that obesity and type 2 diabetes are associated in both clinical and epidemiological studies (column 1, lines 29-31) and that weight reduction is often recommended as the first course of action for patients suffering from Type II diabetes (column 1, lines 42-45). Therefore, one having ordinary skill in the art would have been motivated to practice a weight reduction method of treatment to treat obese patient who is Suffering from Type II diabetes.

Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the treatment of Bachynsky in view of Rink et al. with compound modifications in view of Batt et al. to result in the practice of the instant invention with a reasonable expectation of success.

The recitation of the compound having a slope calculated from an equation as defined in claims 1-2, 4-7 and 14-17 is merely a characterization of the compound and therefore does not limit the claims.

With respect to the recitation of "increasing mitochondrial respiration" in the claims, when the same compound is administered to treat the same patient population, the mechanism of

action of "increasing mitochondrial respiration" is expectedly present.

Regarding the recitation of claim 14, since there is no extra active step in the method of treatment for conducting the Assay, the compound being a chemical uncoupler as defined is merely a characterization of the compound and therefore does not limit the claim.

Regarding the recitation of claim 15, since the nitro group of the prior art compound is the same nitro group of the instant compound, the fact that the nitro group is a cation is merely a characterization of the compound and therefore does not limit the claim.

Response to Arguments

8. Applicant's arguments filed May 14, 2007 have been fully considered but they are not persuasive.

In response to the applicant's argument that the submitted prodrug forms of the compounds of the present invention are readily synthesized with appropriate experimentation available in the art, the examiner determines that due to lacking chemical structural information for what they are and chemical structures are highly variant and encompasses a myriad of possibilities, the skilled artisan cannot envision the detailed chemical structure of the encompassed prodrugs, regardless of the complexity or simplicity of the method of isolation. To the extent that no structure function data is disclosed in connection with these functionally described compounds to correlate, or there is not disclosed correlation established between these functional drugs and the contemplated desired therapeutic effect to be achieved in practicing the instant invention, the specification provides insufficient written description to support the genus encompassed by the claims.

Although the claims 1-2, 4-7 and 14-17 were rejected under 112, 1st paragraph, for scope of enablement, applicant presented no argument to the examiner's contentions. In absence of applicant's arguments to this issue, the examiner maintains the previous rejection. The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Batt provides ample motivation to substitute a nitro group of the prior art compound

Art Unit: 1614

with aceto group with the expectation that the substitution would not significantly alter the analogous properties of the compound due to close structural similarity of the compounds.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. No Claim is allowed.

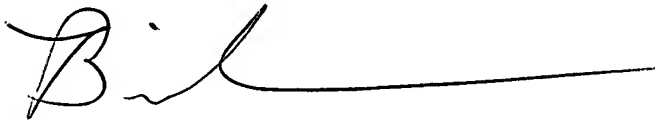
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see <http://pair-direct.uspto.gov> Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Primary Patent Examiner
AU 1614

A handwritten signature in black ink, appearing to be 'B. Kwon', followed by a long horizontal line extending to the right.